Cohort Multiple randomized controlled trials open-label of immune modulatory drugs and other treatments in COVID-19 patients

CORIMUNO-19

INTERVENTIONAL RESEARCH PROTOCOL INVOLVING HUMAN PARTICIPANTS CONCERNING MULTIPLE IMMUNE REGULATORY MEDICATIONS FOR HUMAN USE

CORIMUNO-ANA: Trial Evaluating Efficacy Of Anakinra In Patients With Covid-19 Infection, Nested In The CORIMUNO-19

Global project code number: APHP200375

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SYNOPSIS

Title	**CORIMUNO-ANA: TRIAL EVALUATING EFFICACY OF ANAKINRA IN PATIENTS WITH COVID-19 INFECTION, NESTED IN THE CORIMUNO-19 COHORT**
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Sponsor of the study	**Assistance Publique-Hôpitaux de Paris**
Study phase	**Phase 2**

CORIMUNO-ANA: TRIAL EVALUATING EFFICACY OF ANAKINRA IN PATIENTS WITH COVID-19 INFECTION, NESTED IN THE CORIMUNO-19 COHORT

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For the Immune COVID-19 group

1. General comment on using of Anakinra alone or in combination with anti-viral drugs in CORIMUNO protocols:

As further discussed in the rationale of this protocol, it seems interesting to use anakinra (ANA) (Kineret®), a recombinant human decoy IL-1Ra blocking both IL-1α and IL-1β, in severe patients infected with Covid-19 just before or after intensive care unit (ICU) transfer in order to avoid or to interrupt the cytokine release phase.

Moreover, it appears very interesting to test the association of anakinra with an anti-viral agent at a stage of the disease where the viral load is high, i.e. in the group of patients not hospitalized in ICU. Indeed, in these non-ICU patients, it is appealing to evaluate the combination of two complementary approaches in order to reduce the need of ventilator utilization (including non-invasive ventilation) and thus the overload of ICUs thanks to a double action:

- to control the viral replication with an antiviral with the aim to limit the source of the hyperinflammatory state
- and to potentialize this effect using a specific immune modulator targeting the cytokine IL-1, as one of the first trigger of pathophysiology.

Favipiravir is an organo-fluorinated pyrazine used as an antiviral against RNA viruses (Jordan PC et al, Antiviral Chemistry and Chemotherapy 2018; Dong L et al, Drug Discoveries & Therapeutics. 2020, approved for the treatment of flu in China and Japan. Favipiravir was recently tested in COVID-19 patients in an open-label control study in combination with inhaled beta-interferon (Q. Cai et al, Engineering; 2020). While the number of patients was low (80), use of Favipiravir was associated with statistical virologic (duration of viral clearance) and radiological (chest imaging) benefits when compared with the control arm (Ritonavir/Lopinavir).

Thus, this first protocol CORIMUNO-ANA will evaluate the efficacy of ANA alone in both types of patients hospitalised or not in ICU.

Another companion protocol (CORIMUNO-ANAFAVI) will be submitted further in non-ICU patients for testing the association of Anakinra and Favipiravir vs Favipiravir alone. In non-ICU patients, the data from the two protocols will be pooled allowing to assess the evolution of 4 groups of 30 non-ICU patients each:

- Anakinra alone
- Favipiravir alone
- Anakinra + Favipiravir
- Standard of care

We now detail the first protocol CORIMUNO-ANA that evaluate the efficacy of ANA alone versus standard of care in both types of patients hospitalised or not in ICU.

2. Rationale for IL-1 involvement in COVID-19

2.1 Inflammation in COVID-19 infection

Coronaviruses (CoVs) have caused a major outbreak of human fatal pneumonia since the beginning of the 21st century. CoVs are enveloped viruses with a positive RNA genome, belonging to the Coronaviridae family of the order Nidovirales, which are divided into four genera (α, β, γ, and δ). The SARS-CoV-2 belongs to the β genus. CoVs contain at least four structural proteins: Spike (S) protein, envelope (E) protein, membrane (M) protein, and nucleocapsid (N) protein.
Severe acute respiratory syndrome coronavirus (SARS-CoV) broke out and spread to five continents in 2003 with a lethal rate of 10% (1). The Middle East Respiratory Syndrome Coronavirus (MERS-CoV) broke out in the Arabian Peninsula in 2012 with a fatality rate of 35%. (2, 3)

SARS-CoV 2 or Coronavirus disease 2019 (COVID-19) is a world pandemic carrying a mortality of approximately 3.7%. Because Wuhan Viral Pneumonia cases were discovered at the end of 2019, the coronavirus was named as 2019 novel coronavirus or "2019-nCoV" by the World Health Organization (WHO) on January 12, 2020 (4). Since 2019-nCoV is highly homologous with SARS-CoV, it is considered a close relative of SARS-CoV. The International Virus Classification Commission (ICTV) classified 2019-nCoV as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) on February 11, 2020. At the same time, WHO named the disease caused by 2019-nCoV as COVID-19. Common symptoms of a person infected with coronavirus include respiratory symptoms, fever, cough, shortness of breath, and dyspnea. Case severity and mortality substantially increase with age. Comorbidities, particularly the presence of cardiovascular diseases are an aggravating factor (5).
The reason the marked heterogeneity in individual sensitivity to COVID-19 NCP and the potential roles of ageing and comorbidities is currently unknown.
There is currently no specific medicine or treatment for diseases caused by SARS-CoV-2/COVID-19.

Such severe clinical condition displayed by some of the patients affected with COVID-19 pneumonia are strongly reminiscent of previous and recent epidemic cases of respiratory failure associated to related coronarovirus such as the MERS-CoV, SARS-CoV.
In more severe cases, infection can cause pneumonia, severe acute respiratory syndrome, kidney failure, and even death (6). Death results from respiratory failure and is associated in a

substantial percentage of patients with an inflammatory syndrome and a cytokine storm (7) with acute respiratory distress syndrome (ARDS) and features of macrophage activation syndrome/hemophagocytic lymphohistiocytosis (HLH) that should be better defined.

The innate immunity is the first line of defense that recognizes infection and initiates the process of pathogen clearance and tissue repair.
IL-1 exists in two isoforms: IL-1α, a membrane-bound, autocrine, and paracrine messenger, and IL-1β, a soluble, autocrine, paracrine, and endocrine messenger. Both isoforms bind the IL-1 receptor (type I) and recruit the accessory and adaptor proteins to amplify the inflammatory response through the disinhibition of the effects of I-κB of the nuclear factor κB. IL-1β is produced through the inflammasome cascade, one of the most important complexes which participates in pathogen clearance. The inflammasome is a multi-protein complex that recruits pro-caspase-1 via ASC (the adaptor molecule apoptosis-associated speck-like protein containing a CARD) and then proceeds to cleave the cytokine precursors pro-IL-1β and pro-IL-18 into mature IL-1β and IL-18. Importantly, Interleukin-1α acts primarily as an alarmin and initiates the inflammatory cascade, including the production of IL-1β, which in turn further amplifies the inflammatory response.

Upon activation, the inflammasome also promotes an inflammatory form of cell death named pyroptosis, which is regulated by the N-terminal domain of gasdermin D (GSDMD) by forming pores in the plasma membrane.
A significant increase in IFN-γ and the pro-inflammatory cytokines IL-1β, IL-6 and IL-12 has been reported for at least 2 weeks after disease onset in SARS patients despite treatment with corticosteroids (8). Furthermore, high concentrations of tumor necrosis factor/TNF-α, interleukin/IL-1β, and IL-6, were detected in autopsy tissues (9). Although dysregulation of inflammatory cytokines may be involved in lung injury and the pathogenesis of SARS-CoV, the underlying molecular mechanisms are not fully understood.
A recent report indicates higher serum IL1 β and IL1R α in both ICU patients and non-ICU patients with pneumonia than in healthy adults at initial assessment (6). Of note, no difference in mean IL-1β levels were found between the ICU patients and non-ICU patients with pneumonia.

2.2- Mechanisms of activation of inflammasome in COVID-19 infection

The viruses themselves may activate the inflammasome.
The innate immune system is sensitive to pattern recognition receptors (PRRs) to detect pathogen-associated molecular patterns (10-12). Recognition of virus infection plays an important role in limiting virus replication at the early stages of infection. Nod-like receptor family, pyrin domain-containing 3 (NLRP3) is activated by a wide variety of stimuli, including virus infection (13). Once assembled, the NLRP3 inflammasome triggers the auto-cleavage of pro-caspase-1. As an effect factor, caspase-1 mediates the proteolytic processing of pro-IL-1β, pro-IL-18, and the propyroptotic factor gasdermin D (GSDMD). GSDMD forms pores in the membrane of infected cells, facilitating the secretion of IL-1β/IL-18 and inducing the inflammation-associated cell death known as pyroptosis. The secretion of IL-1β subsequently recruits neutrophils to the inflammatory site to aid in the elimination of invading viruses. Moreover, both IL-1β and IL-18 are responsible for the subsequent induction of the adaptive immune response. Accordingly, optimal activation of the NLRP3 inflammasome facilitates the establishment of a host antiviral status.

However, aberrant NLRP3 inflammasome activation can also lead to severe pathological injury. In an IAV infection model, juvenile mice had sustained elevated levels of type I IFNs and persistent NLRP3 inflammasome activation, suffering from severe lung injury independent of viral titer (19). In addition, HIV-1 infected microglia are shown to cause NLRP3-associated neuroinflammation (20). Such overactivation of the inflammasome may be triggered by viral proteins, such as E protein from SARS-CoV, that causes the flux of calcium from intracellular storages to the cytosol, which is indispensable for NLRP3 activation (14). Likewise, infection with an RNA virus was shown to initiate assembly of the RIP1-RIP3 complex, which promoted activation of the GTPase DRP1 and its translocation to mitochondria to drive mitochondrial damage and activation of the NLRP3 inflammasome (15). Furthermore, viroporins, transmembrane pore-forming viral proteins, are involved in virus-induced NLRP3 inflammasome activation. The SARS-CoV 3a viroporin activates the NLRP3 inflammasome through an ion channel activity. SARS-Cov induced K+ efflux and mitochondrial reactive oxygen species were important for SARS-CoV 3a-induced NLRP3 inflammasome activation (16).

Amplification of pro-inflammatory cytokines and interleukins may originate from immune cells. Severe and critical COVID-19 pneumonia share features of "cytokines storm" such as seen in severe cytokine release syndrome (CRS), which is characterized by fever, hypotension and respiratory insufficiency associated with elevated serum cytokines, including IL-1β and IL-6, in large part derived from myeloid cells (17). In the setting of CAR T cell–derived cytokines, IL-1β is produced by recipient macrophages (18). Zhou Y et al. recently reported inflammatory CD14+CD16+ monocytes suggesting excessive activated immune response caused by pathogenic GM-CSF+ Th1 cells that may connect pulmonary immunopathology leading to deleterious clinical manifestations after COVID-19 infections (https://doi.org/10.1093/nsr/nwaa041; 13/03/2020).

A parallel route for accentuated IL-1β in sepsis are the neutrophils that have been proved to be the main source of IL-1β in the infection (19). Excessive neutrophil pyroptosis is obviously harmful in the early hyperinflammatory state in sepsis. in severe sepsis, the release of various enzymes, inflammatory mediators in heart, lung, kidney and other vital organs by a large number of activated neutrophils, but with chemotactic dysfunctions, leads to tissue cell damage, and ultimately to the development of multiple organs function failure (20). Accordingly, antagonism of the IL-1 pathway using Anakinra, an IL-1Ra derivative decoy was proposed to treat CRS. High IL-1β levels directly foster capillary leaks and cells death (pyroptosis) in tissues and indirectly promote amplifying loops such as secretion of IL-8 from human mast cells (21, 22).

3. Investigational medicinal product: ANAKINRA KINERET® (100mg)

3.1 Mechanism of action and Indication of Anakinra

Anakinra (ANA) (Kineret®) is a recombinant human decoy IL-1Ra and therefore blocks IL-1α and IL-1β. Anakinra has a half-life of 4–6 h and is administered subcutaneously once daily for the treatment of rheumatoid arthritis, juvenile arthritis, and gouty arthritis. Anakinra is also approved for cryopyrin-associated period syndromes (CAPS), rare genetic syndromes characterized by enhanced NLRP3 inflammasome activity resulting in elevated IL-1β levels.
In CAPS, the recommended anakinra dose is 1-2 mg/kg, but it is often up titrated to response 3-4 mg/kg. Anakinra's short half-life may be advantageous as doses can be up- or down-titrated

on a daily basis and, if an adverse effect occurs, the drug is cleared from circulation within 24 h. However, subcutaneous injection of anakinra causes local injection site reactions such as pain and erythema in ~20% of patients that lead to discontinuation in ~5%.

Anakinra has also been used at higher dose with an IV regimen in the management of critically ill adult patients with haemophagocytic lymphohistiocytosis (23).

Lastly, two randomized controlled studies have evaluated efficacy of Anakinra in severe sepsis at mega dose: 2 mg/kg/hr for 72 hours continuously, i.e. between 3,000 mg and 4,000 mg / day! (24, 25, 26). The first phase 2 study was positive with a slight advantage in term of 28-day mortality in the Anakinra group vs placebo (24). However, in the large phase III study having included 900 patients, there was no advantage of survival in the Ankinra group at 28 days: 29.7% and 30.5% in the Anakinra and placebo groups, respectively (25). But a post-hoc analysis showed that the 28-day mortality in hepatobiliary dysfunction (HBD)/disseminated intravascular coagulation (DIC) patients who received Anakinra was significantly lower (34.6%) than was noted for HBD/DIC patients who received placebo (64.7%, p = 0.0006), corresponding to a 47% reduction in mortality associated with Anakinra (26). In none of these studies, there was no safety signal compared to the placebo group.

3.2 Safety of Anakinra and of other IL-1 antagonists

IL-1 blockers reduce the leucocyte and neutrophil counts, but rarely to the level of severe neutropenia (<500/mm3), and the leucocyte cell count does not appear to correlate with the risk of infection.

While IL-1 blockers are generally well tolerated, and without direct organ toxicity, their use can complicate the presentation and clinical course of an infection, and they have been associated with an excess of infection-related deaths. Likewise, in registry studies, the concomitant use of IL-1 blockade as an add-on to immunosuppressants such as prednisone and/or methotrexate in patients with rheumatoid arthritis is associated with increased risk of serious infections (27).
However, the excess risk of fatal infection with IL-1 blockade is rather small in absolute terms. In more than 30 000 patient-years of treatment with canakinumab in CANTOS, there was an excess of only 1.3 fatal infections per 1000 patient-years (number needed to harm 769)(28).

Of note, the use of IL-1 blockers is not associated with an increased risk of opportunistic infection.

Lastly, in the studies using Anakinra at very high dose IV in sepsis (24, 25, 26) and in critically ill adult patients with haemophagocytic lymphohistiocytosis (23), there was no specific safety signal compared to placebo.

3.3 Justification of the schedule proposed for this nested trial

It is known that macrophages/monocytes produce IL-1 upon activation, and IL-1 in turn can elicit production of IL-6 by the macrophages/monocytes (18). Thus, prevention of IL-1R activation at early stages is expected to blunt IL-6 and IL-8 secretion. Thus, it is reasonable to

consider IL-1 antagonism, just before or at the time of the cytokines storm, for preventing or alleviating the occurrence or severity of COVID-19-associated CRS and ARDS.

In severe auto-inflammatory syndromes, it has been proposed to increase the daily dose up to 4 mg/kg/day or maximum 8 mg/kg in children, corresponding to around 300 to 500 mg/day SC in adults on a daily basis. In the 3 trials in sepsis, a mega dose 10-fold higher has been used in continuous IV injection for only 3 days.

A trial of Anakinra is planned to begin in Italy in critically ill patients infected with COVID-19 with biomarkers of bad prognosis. The proposed schedule is an IV infusion of 400 mg/day in total, divided into 4 doses of 100mg given every 6 hours for 14 days.

Actually, the cytokine storm in COVID-19 infection occurs between D7 and D10 and rarely lasts more than 3 days.

Thus, we propose as a schedule the dose proposed by the Italian group: 400 mg/day, but only for 3 days, and with a progressive decrease at 200 mg/day at D4 and 100 mg/day at D5 and stop thereafter. In case of absence of improvement at D4 (absence of clinical improvement AND absence of decrease of CRP level > 50%), we propose 3 supplementary days of treatment at 400 mg/day at D4, D5 and D6 and a decrease at 200 mg/day at D7 and 100 mg/day at D8 and stop thereafter.

Since the SOBI Company is aware of unpublished data showing that the distribution of the drug is better in hyper inflammatory states with an IV infusion and since it is logical to use the same route of administration as in the Italian study, we have chosen an IV infusion of 400 mg / day.

Since we want to avoid too many entries in the room of the patients by the nurses, and since the SOBI Company is aware of unpublished data showing that the PK and distribution of two daily 1-hour IV infusions of 200 mg are close to those of 4 daily 1-hour infusions of 100 mg, we have chosen to use in our study two daily 1-hour IV infusions of 200 mg

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4. The CORIMUNO-ANA protocol:

ANAKINRA KINERET® (100mg) will not be specifically provided by the sponsor in the context of the COVID 19 pandemic. The drugs will be provided by the hospital pharmacies to the care units based on a specific research prescription.

Origin: Specialty with marketing authorization in UE/France, marketed in France.

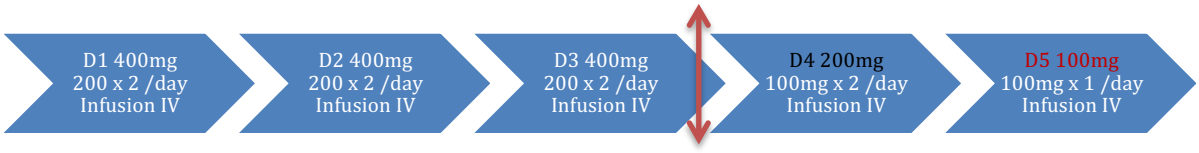
Storage: Store in the refrigerator (between 2 ° C and 8 ° C). Do not freeze.
The pre-filled syringe should be stored in the original package in order to protect from light.

4.1 ANAKINRA KINERET® Posology and drug administration

4.1.1 Posology

Treatment includes the administration of Two IV infusions / day of **ANAKINRA KINERET® 200mg (Total 400 mg)** at day 1 (D1), D2 and D3, two IV infusions / day of **ANAKINRA KINERET® 100mg (Total 200 mg)** at day 4 (D4), and one IV infusion of **ANAKINRA KINERET® 100mg (Total 100 mg)** at day 5 (D5).

Administration schedule if satisfactory clinical and biological response on D4 (see more details in addendum on page 27)



Evaluation

In case of absence of improvement at D4 (absence of clinical improvement AND absence of decrease of CRP level > 50%), **3 supplementary days of treatment at 400 mg/day will be done at D4, D5, D6 followed by a decrease at 200 mg/day at D7 and 100 mg/day at D8 and stop thereafter**

Administration schedule if absence of improvement on D4 (see more details in addendum on page 27)

Evaluation

4.1.2 Administration

We recommend preparing the investigational medicinal product by administering the contents of the 200 or 100 mg Anakinra syringe(s) directly into a 100 mL bag of 0.9% NaCl, based on the data reported by SOBI (cf. attached document "Memo on dilution of Kineret in 0.9% NaCl").

The final concentration in the bag containing diluted anakinra will therefore be from 1mg / mL (if administration of 100mg) to 2mg / mL (if administration of 200mg).

The IV administration of Anakinra should take place within 4 hours after the preparation over a 60 minute infusion period.

Anakinra should not be infused simultaneously with other agents, and other products must not be added to the infusion bag.

4.1.3 Traceability in investigational centres

In accordance with the rules of Good Practices and to track the treatment given to each patient, all the information related to the treatment will be collected on a traceability sheet (Preparation, Dispensation, Date of administration, Time of administration, Batch number and expiry date, and Dose administered).

4.1.4 Methods for monitoring compliance with the treatment

To track the treatment given to each patient, all the information related to the treatment will be collected on a traceability sheet. This sheet will be prospectively and exhaustively monitored by clinical research assistants during the study. In case of deviations from the protocol there will be reminders to the centers and regular checks.

4.2 Treatment in Control arm

Control patients will receive the best standard of care.

4.3 Inclusion/Exclusion criteria for the CORIMUNO-ANA nested trial

Inclusion Criteria:

1. Patients included in the CORIMUNO-19 cohort

2. Patients with C-reactive protein level (CRP) > 25 mg / L the day or the day before the infusion)

2. Patients belonging to one of the 2 following groups:

- - Group 1: Cases meeting all of the following criteria

- *Requiring more than 3L/min of oxygen*
- *OMS/WHO progression scale = 5*
- *No NIV or High flow*

- Group 2: Cases meeting all of the following criteria

- *Respiratory failure AND (requiring mechanical ventilation OR NIV OR High flow)*
- *OMS/WHO progression scale >=6*
- *No do-not-resuscitate order (DNR order)*

Exclusion Criteria:

- Patients with exclusion criteria to the CORIMUNO-19 cohort.
- Known hypersensitivity to Anakinra or to any of their excipients.
- Pregnancy
- Current documented bacterial infection.
- Patient with any of following laboratory results out of the ranges detailed below at screening:
    - Absolute neutrophil count (ANC) ≤ 1.0 x 10^9/L
    - Haemoglobin level: no limitation
    - Platelets (PLT) < 50 G /L
    - SGOT or SGPT > 5N
    - Severe renal insufficiency with Glomerular filtration rate < 30 ml / mn

4.4 Number of patients

- In group 1 (Non-ICU patients)
  60 patients randomised to Anakinra
  60 patients randomised to standard of care

- In group 2 (ICU patients)
  60 patients randomised to Anakinra
  60 patients randomised to standard of care

4.5 Endpoints for the trial

4.5.1 Efficacy endpoints

Measures

A core set of clinical measures will be recorded daily the first 2 weeks and then every week. The core measures include measures of OMS progression scale, oxygenation, mechanical ventilation. For patients who are eligible for an intervention trial (in both the intervention and control arms), this days measurement will include trial-specific measures related to the trial outcomes of interest.

Primary and secondary endpoints:

The primary endpoint and secondary endpoints will depend on the group of patients and tested medication.

For the group 1 of patients *not requiring ICU*:

Co Primary Endpoints

Group 1:

Co-primary endpoints:

1. Survival without needs of ventilator utilization (including **non invasive ventilation and high flow**) at day 14. Thus, events considered are needing ventilator utilization (including Non Invasive Ventilation, NIV or high flow), or death. New DNR order (if given after the inclusion of the patient) will be considered as an event at the date of the DNR.
2. Early endpoint : proportion of patients alive without non-invasive ventilation of high low at day 4 (WHO progression scale ≤ 5). A patient with new DNR order at day 4 will be considered as with a score > 5.

OMS/WHO Progression scale	Descriptor	Score
Uninfected	Uninfected; non-viral RNA detected	0
Ambulatory	Asymptomatic; viral RNA	1

	detected	
Ambulatory	Symptomatic; Independent	2
Ambulatory	Symptomatic; Assistance needed	3
Hospitalized : mild disease	Hospitalized; No oxygen therapy	4
Hospitalized : mild disease	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized : severe disease	Hospitalized; oxygen by NIV or High flow	6
Hospitalized : severe disease	Intubation and Mechanical ventilation, pO2/FIO2>=150 OR SpO2/FIO2>=200	7
Hospitalized : severe disease	Mechanical ventilation, (pO2/FIO2<150 OR SpO2/FIO2<200) OR vasopressors (norepinephrine >0.3 microg/kg/min)	8
Hospitalized : severe disease	Mechanical ventilation, pO2/FIO2<150 AND vasopressors (norepinephrine >0.3 microg/kg/min), OR Dialysis OR ECMO	9
Death	Dead	10

Secondary end-points will be OMS progression scale at 4, 7 and 14 days, overall survival at 14, 28 and 90 days, time to discharge, time to oxygen supply independency, time to negative viral excretion.
Biological parameters improvement:
Estimated GFR, CRP, myoglobin, CPK, cardiac troponin, ferritin, lactate, cell blood count, liver enzymes, LDH, D-Dimer, albumin, fibrinogen, triglycerides, coagulation tests, urine electrolyte, creatinuria, proteinuria, uricemia, IL6, procalcitonin, immunophenotype (Annexe 2), and exploratory tests (Annexe 3).

For the group 2:

Co Primary Endpoints

1. Cumulative incidence of successful tracheal extubation (defined as duration extubation > 48h) at day 14 if patients have been intubated before day 14 ; or removal of NIV or high flow (for > 48h) if they were included under oxygen by NIV or High flow (score

6) and remained without intubation. Death or new DNR order (if given after the inclusion of the patient) will be considered as a competing event.
2. Early end point: proportion of patients with a decrease of WHO score of at least 1 point at day 4.

Secondary end points will be OMS progression scale at 4, 7 and 14 days, overall survival at 14, 28 and 90 days, the 28-day ventilator free-days, the evolution of PaO2/FiO2 ratio, respiratory acidosis at day 4 (arterial blood pH of <7.25 with a partial pressure of arterial carbon dioxide [$Paco_2$] of ≥60 mm Hg for >6 hours), time to oxygen supply independency, duration of hospitalization, time to negative viral excretion, time to ICU and hospital discharge.

Biological parameters improvement (estimated GFR, CRP, cardiac troponin, urine electrolyte and creatinine, proteinuria, uricemia, IL6, myoglobin, KIM-1, NGAL, CPK, ferritin, lactate, cell blood count, liver enzymes, LDH, D-Dimer, albumin, fibrinogen, triglycerides, coagulation tests (including activated partial thromboplastin time), procalcitonin, immunophenotype (Annexe 2), and exploratory tests (Frozen samples Annexe 3). Rate of renal replacement therapy, ventilation parameters.

Post-hoc analysis in group 1 and in group 2 patients independently and in common
Since biomarkers of inflammation and others may be associated with the cytokine storm and possibly with response to ANA, post-hoc analysis will be performed in patients with high and low CRP, and in patients with increased of other inflammation biomarkers.

Primary and secondary end-point in patients with
Increased CRP between 25 and 100 mg / L
Increased CRP > 100 mg / L

Primary and secondary end-point in patients with all 3 following biomarkers
Increased LDH
Increased D Dimers
Increased Ferritin

Primary and secondary end-point in patients with one of the 3 following biomarkers
Increased LDH
Increased D Dimers
Increased Ferritin

4.5.2 Safety endpoints

In the setting of COVID-19 NCP and short-term immunomodulatory therapy, we will monitor major safety endpoints: blood cells and platelets counts and liver transaminases, frequently, every three days systematically.

- **Neutrophil count**

Treatment with Anakinra was associated with a higher incidence of decrease in ANC. Decrease in ANC was not associated with higher incidence of infections, including serious infections.

- In patients who develop an ANC less than 1 x 10^9/L, treatment with Anakinra should be discontinued.

- **Platelet count**

  Treatment with Anakinra was associated with a reduction in platelet counts in clinical studies.

  - In patients who develop a platelet count less than 50 x 10^3/ µL, treatment with Anakinra should be discontinued.

- **Liver enzymes**

  Treatment with Anakinra was associated with a higher incidence of transaminase elevations.

  - In patients who develop elevated ALT greater than 5 x ULN, treatment with Anakinra should be discontinued

- **Hypersensitivity reactions**: monitoring of occurrence of skin rashes, drop of blood pressure, ventilatory asynchronization. At the time of treatment injection.

4.5.3 Specific data to be collected for this trial

None

4.4.4 Expected benefits and risks

The clinical benefit is globally to prevent death in all patient groups.

Other benefits are to:

- blunt not only the pneumopathy-induced damage but also other COVID-19-associated injuries such as acute kidney injury (AKI), myocarditis, secondary bacterial infections.

- shorten the duration of hospital stay with minimization of physical (hospital acquired pressure ulcers, increased morbidity and mortality associated with nosocomial infections), psychological and economic complications related with prolonged stay.
- Shortening the hospital stay fosters not only individual clinical benefit but also collective clinical benefit through facilitation of collective access to caregivers.
- limit long term sequelae, in particular lung fibrosis and chronic kidney disease secondary to acute kidney injury (markedly prevalent in about 20% of individuals with ARDS).

The risks pertain to potential adverse effects of Anakinra and especially there is a concern that IL-1 inhibition may exacerbate infections.
However, there are currently two randomized controlled trials of Anakinra in sepsis. In none of them, there was an increased incidence of secondary sepsis in the Anakinra arm vs the placebo arm.
Treatment with Anakinra was also associated with a reduction in platelet counts, neutrophils counts and hypersensitivity reactions, including anaphylaxis.

4.6 Statistical methods

4.6.1 Principles of cohort multiple randomized controlled trials

The key features of the cohort multiple Randomized Controlled Trials (cmRCT) design are:
(I) Recruitment of a large observational cohort of patients with the condition of interest
(II) Regular measurement of outcomes for the whole cohort
(III) Capacity for multiple randomised controlled trials over time
Patients enrolled in the cohort agree to allow their longitudinal data to be used in the aggregate. They also allow their data to be used to identify them to be invited to participate in research interventions or for comparison purposes for intervention trials that may be conducted with other patients while they are participating in the cohort.
In the cmRCT design, only eligible patients randomly selected to be offered an intervention, are contacted and offered treatment. Eligible patients not
selected to be offered an intervention are not notified about this trial and will be in the control group. Consent for specific trials will be obtained from those eligible patients who are invited and accepted the offer to participate. In the cmRCT design, as described to patients when they consent to participate in the cohort, only eligible patients randomly selected to be offered an intervention, but not eligible non-selected patients, are contacted and offered treatment.

Eligible patients not selected are not notified about the trial. Consent for specific trials will be obtained from those eligible patients who are invited and accept the offer to participate. Post-intervention outcomes among eligible patients who accept the offer to receive the intervention will be compared with outcomes among patients from the cohort who were identified as eligible for the intervention, but were not randomly selected to be offered the intervention and not contacted about the intervention.

In the context of the COVID crisis, the advantage of the cmRCT design to conduct multiple trials that draw participants from the same patient cohort is important given the imperative that we have to answer multiple research questions (some identified and others not yet identified) in a very short time (a few weeks).

4.6.2 Planned statistical methods, including the timetable for any planned interim analyses

For the CORIMUNO-19-ANA trial, individuals in the cohort eligible in the participating centers are randomized 1:1 until a predefined sample size is reached. **An interim analysis is performed at mid-trial, but inclusions are not frozen to wait for the interim analysis.**

The methods outlined thereafter describe the principles for analyzing the trial in one specific stratum (patients not requiring ICU or patients requiring ICU). The trials are analyzed and conducted separately in each stratum (group 1: patients not requiring ICU and group 2, patients requiring ICU).

One crucial feature of CORIMUNO-19 trials is to remain as flexible as possible, in an urgency context, when information may change quickly. The study therefore attempts to maximize information from limited data generated, while allowing rapid decision. This will be achieved by the use of Bayesian monitoring of the trial. While using a Bayesian approach, where standard definition of type I and II error rate do not apply, the trial is also planned to control for frequentist (i.e. non-Bayesian) error rates. In particular, the overall strategy will be to control for a frequentist one sided type I error rate close to 5% over one specific trial.

The analysis will therefore rely on computing the posterior distribution of the hazard ratio between the experimental and control arms for time-to-event co-primary outcomes and the posterior distributions of event rates in each arm for binary co-primary outcomes. From the latter, the posterior distribution of the difference in event rate will be derived. These posterior distributions will be graphically displayed, and summarized by their medians and 95% credibility intervals (the Bayesian counterparts of confidence intervals).

In a Bayesian analysis, the specification of the prior distribution is crucial. For the CORIMUNO-19-ANA trial, we want the conclusions to depend primarily on data from the

trial, not on prior opinion. An uninformative prior for the hazard ratio will therefore be used. More precisely, the prior distribution for the log hazard ratio will be a Gaussian distribution with mean 0 and variance 10^6. For binary outcomes, let p denote the probability of outcome in a given arm; the prior distribution of p is set as a beta prior distribution with parameters 1 and 1, equivalent to a uniform distribution on the interval (0,1). This corresponds to a hypothetical situation where we would have data on two individuals treated with the corresponding arm strategy, and observing that exactly 1 of the 2 experiencing the outcome. These prior distributions ensure very little influence of our prior opinion on conclusions.

For now, the calculations in this protocol have been performed for a sample size of 60 individuals per arm, with interim analyses after 30. However, this may be adapted to allow continuing the trial if results are promising, though not formally achieving the predefined efficacy boundary. Additional calculations have therefore been performed with the additional recruitment of 30 individuals per arm after the total sample size of 120 has been reached (see below). This may also be modified in future protocols.

Baseline characteristics will be described with summary statistics, namely frequencies and percentages, or medians and interquartile ranges (IQR). Secondary and safety outcomes will be analyzed in a frequentist framework. Final analysis will account for randomization stratification factors. All the analyses will be described in a statistical analysis plan (SAP) that will be written and signed before freezing of the database.

At the end of the study subgroup analyses will be performed according to antiviral therapies. Moreover interactions between experimental treatments and antiviral therapies will explored and tested.

4.6.2 Statistical criteria for termination of the study

This section describes the Bayesian monitoring of the trial in the base protocol. We defined two co-primary outcomes, one time-to-event outcome evaluated up to day 14, and an early success outcome evaluated on day 4. Methods for trial monitoring have been developed for the early outcome because (1) short-term outcomes are obtained more quickly so are easier for early interim decision and (2) calculations of all possible outcomes are more tractable for binary outcomes. For analyses based on the hazard ratio, which allow to account for all information gathered in the trial (even for patients who do not have the entire follow-up necessary to evaluate a binary outcome), the same decision boundaries will be used. It is not expected that the properties of the boundaries would be significantly different when using the posterior distribution of the hazard ratio (similarly to the use of O'Brien Fleming boundaries in frequentist trials for continuous, binary or survival outcomes). More comprehensive simulation

studies will be performed to describe the properties of the design in an appendix to the protocol. Also, in all what follows, we assume the "event" corresponding to the outcome being detrimental to patients, so that an effective treatment would lower the event rate, or achieve a hazard ratio $\theta < 1$. When the clinical definition of the outcome is opposite, then analysis will be performed on the inverse (e.g. failure instead or success, or inverse of the hazard ratio $1/\theta$). Let us denote p_E and p_C the event rates in the experimental and control arms, respectively. At the interim analysis, the posterior probability of a lower event rate in the experimental than in the control arm is calculated, i.e. $P(p_E < p_C \mid \text{data})$, which we term the posterior probability of efficacy. The posterior probability $P(p_E < p_C - \delta \mid \text{data})$ is also computed, corresponding to the probability to achieve at least a d treatment effect, termed the posterior probability of sufficient efficacy. At each interim analysis, if the posterior probability of sufficient efficacy is less than 0.20, the trial may be stopped for futility upon decision of the DSMB (indicative and not binding futility boundary). If the posterior probability of efficacy is higher than 0.99, then the trial may be stopped for efficacy (again this boundary is not binding and the DSMB may propose to continue the accrual based on other information, such as secondary outcomes or safety). The choice of interim monitoring for futility based on the posterior probability of sufficient efficacy and not the posterior probability of efficacy is justified by the need to increase the chance of early stopping for futility when information increases, if the experimental treatment is no better than the control. Conversely, keeping a constant futility boundary on the posterior probability of efficacy would decrease the chances of early stopping if additional analyses are performed, because under the null, as information increases, the posterior distribution of efficacy would converge to 0.5. This boundary is stricter than using a boundary on the posterior probability of efficacy (grey line on the figure 1, left panel), but this choice is justified by the need to quickly identify treatments with a large effect. The futility threshold (0.20) may be revised in future trials, if expected effects are lower.

When no stopping for futility or efficacy is decided, additional patients are recruited in each arm. At the interim analyses, the predictive probability of achieving a success after inclusion of a total of 60 patients per arm (posterior probability of efficacy > 0.95) will also be computed, and the trial can be stopped for futility if it is less than 10%. The final analysis will occur after final recruitment, and a posterior probability of efficacy higher than 0.95 will be considered as indicating efficacy.

To compute the probability of sufficient efficacy, we assumed that the hazard ratio for time-to-event outcomes should be at least 0.85, which translates to an event rate of 45.5% in the

experimental arm when it is 50% in the control arm. Accordingly, δ was set to 0.055 for calculations with binary outcomes. The table 1 presents the properties of the design under different scenarios, with first stage sample size 60 (30 patients per arm) and second-stage sample size 60 (30 additional per arm). The figure 1 displays the decision boundaries for the early outcome.

Table 1. Operational characteristics of the design under different scenarios.

	Failure rate p in each group			
Scenario	No effect	Very large effect	Large effect	Mild effect
Parameterizations	p_C=0.5, p_E=0.5	p_C=0.5, p_E=0.2	p_C=0.5, p_E=0.3	p_C=0.5, p_E=0.35
Corresponding hazard ratio	1	0.32	0.51	0.62
Probability of early stopping for futility	0.349	0.0017	0.023	0.057
Probability of early stopping for efficacy	0.0087	0.558	0.228	0.121
Probability of efficacy at 2nd stage	0.038	0.413	0.510	0.393
Overall probability of rejection	0.047	0.972	0.739	0.514

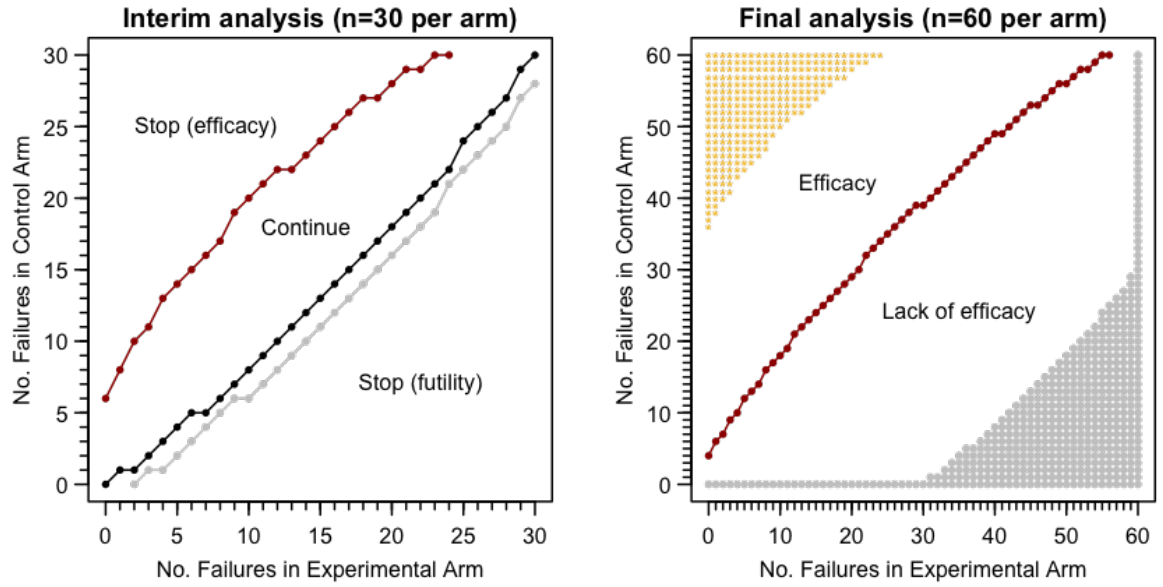


Figure 1. Decision boundaries for the interim and final analysis. Red lines indicate efficacy boundaries, and black lines futility boundaries. On the left plot, the interim analysis is performed after inclusion of 30 patients per arm, and the gray line indicate what the boundary would be if the posterior probability of efficacy was used to define futility instead of the posterior probability of sufficient efficacy. On the right plot, the final analysis after accrual of 30 more patients per arm is presented. Golden stars indicate regions that should not occur if the decision boundaries are respected, because the trial would have been stopped for efficacy at the interim analysis.

Gray points indicate regions that should not occur if the decision boundaries are respected, because the trial would have been stopped for futility at the interim analysis.

In the case the DSMB would deem results promising but not yet conclusive after inclusion of 60 individuals per arm (that we consider for illustration as a posterior probability of sufficient efficacy of 0.40 or more but a posterior probability of efficacy is of 0.97 or less), 30 additional patients per arm could be recruited, the final decision boundary could be adapted to a posterior probability of efficacy > 0.963 to control the type I error rate. The table 2 summarizes the properties of such extension under the four previous scenarios, and illustrates that this could have an important effect on the power in scenarios where the efficacy is less than anticipated.

Table 2. Operational characteristics of the design with extension to a third stage, under different scenarios. In this example, it is assumed that the DSMB would consider results to be promising if the posterior probability of sufficient efficacy of 0.40 or more but a posterior probability of efficacy is of 0.97 or less, and the final decision boundary is set to a posterior probability of efficacy > 0.963 to control the type I error rate.

	Failure rate p in each group			
Scenario	No effect	Very large effect	Large effect	Mild effect
Parameterizations	p_C=0.5, p_E=0.5	p_C=0.5, p_E=0.2	p_C=0.5, p_E=0.3	p_C=0.5, p_E=0.35
Probability of occurrence	0.307	0.046	0.313	0.460
Probability of efficacy at 3rd stage	0.018	0.043	0.209	0.221
Overall probability of rejection	0.050	0.994	0.848	0.631

In terms of trial monitoring, it is also planned that more interim analyses would be performed, primary safety reviews, but the posterior distribution of key efficacy parameters should then also be presented to the DSMB, without formal stopping rules. This may be performed on a weekly basis according to the CORIMUNO cohort protocol, and adapted according to actual accrual in the trial.

4.6.2 Number of participants and justification

The total sample size in each group (group 1: patients not requiring ICU and group 2: patients requiring ICU) is fixed at 120 (60 per arm) for the final analysis, with interim analysis after 60 (30 per arm), and an option to accrue 60 patients more (30 per am) depending of the

recommendations of the DSMB. Overall, the CORIMUNO-19-ANA trial **may therefore accrue between 120 patients and 360 patients in total** (between 60 and 180 in each group of patients).

The calculations shown in the table 1 show that the type I error rate of the design would be 4.7% if the event rate is 0.50 in each arm, and the power to detect a decrease from 0.50 to 0.20 would be 97.2%. This trial would also have power 73.9% to detect a decrease from 0.50 to 0.30.

4.6.2 Anticipated level of statistical significance

The trial is not designed for frequentist statistical testing at a predefined level of statistical significance. Nevertheless, as explained above, the current decision boundaries allow to control for a frequentist type I error rate of 0.047.

4.6.3 Subject replacement strategy

No subject replacement is planned.

4.6.4 Method for taking into account missing, unused or invalid

We do not expect missing data for the primary outcome. However, were data to be missing, they will be imputed as failures for the trial monitoring. No imputation will be used for secondary efficacy and safety outcomes.

4.6.5 Management of modifications made to the analysis plan for the initial strategy

All the analyses will be described in a statistical analysis plan (SAP) that will be written and signed before freezing of the database), in order to accommodate any event or protocol modification that may have occurred and that would affect the way the analysis should be conducted.

We do not expect modifications of the initial analysis strategy. However, should such modifications occur after the SAP has been validated, a modified SAP would be issued. The original SAP as well as the modified SAP will be kept in the study files, with the justification for any modification.

4.6.6 Choice of individuals to be included in the analyses

For interim monitoring, the analysis will be carried out according to the intention to treat (ITT) principle, i.e. each randomised participant will be analysed in the group assigned to him/her by randomisation, regardless of the actual treatment received or other protocol deviations. In particular patients randomised while not meeting eligibility criteria will be kept in the analysis. In the cmRCT design, randomization occurs prior to offering an intervention, and some number of eligible patients who are randomly selected to be offered an intervention will not accept the

offer. An intention to treat analysis could therefore dilute any treatment effects, and Relton et al. suggested using a complier average causal effect (CACE) analysis which provides unbiased estimates of the treatment effect for patients who comply with the protocol.

At the final analysis stage, the ITT will be carried out, comparing all randomised patients in the intervention arm they were allocated to as described above, but a CACE analysis will be added, using an instrumental variable approach which assumes that a patient's decision not to accept the intervention will not affect the outcome (except through the intervention actually received).

4.7. Recording and reporting adverse events

The sponsor, represented by its safety Department, shall continuously assess the safety of each investigational medicinal product throughout the trial.

For serious adverse events likely to be related to the investigational medicinal product:

- Refer to the SmPC of Kineret in Appendix

- **For anakinra:**

The most frequently reported adverse reactions with Kineret are injection site reactions (ISRs), which are mild to moderate in the majority of patients. The most common reason for withdrawal is injection site reaction. The incidence of serious infection is higher in Kineret-treated patients compared to patients receiving placebo. Neutrophil decreases occurred more frequently in patients receiving Kineret compared with placebo.

Addendum

Schéma d'adaptation de doses de l'Anakinra dans l'essai CORIMUNO-ANA.

Le schéma de doses de l'Anakinra dans l'essai est le suivant :

Tous les patients			Répondeurs		Non répondeurs				
			200 mg : **100 mg x2/j**	100 mg x1/j					
D1	**D2**	**D3**							
400 mg : **200 mg x2/j**	400 mg : **200 mg x2/j**	400 mg : **200 mg x2/j**			**D4**	**D5**	**D6**	**D7**	**D8**
					400 mg : **200 mg x2/j**	400 mg : **200 mg x2/j**	400 mg : **200 mg x2/j**	200 mg : **100 mg x2/j**	100 mg x1/j

1. **Définition de la réponse à J4**

Il n'y a pas de définition protocolaire de la réponse à J4 qui permet de poursuivre le traitement à pleine dose 3 jours de plus ou d'entamer la décroissance.

En particulier, il est très important de mentionner que la réponse à J4 qui va motiver la poursuite de la pleine dose ou la décroissance n'a rien à voir avec le critère primaire de réponse rapide utilisé dans l'évaluation.

Pour l'appréciation de cette réponse, le comité de coordination donne les conseils suivants :

- Patients du groupe 1 : La bonne réponse à J4 est définie par une diminution des besoins en oxygène de plus de 50 %. Dans ce cas-là, il est recommandé de débuter la décroissance.

- Patients du groupe 2 : La bonne réponse à J4 est définie par la suppression de l'Optiflow ou de la VNI chez les patients qui bénéficiaient de ce type de ventilation ou par l'extubation pour les patients intubés ou par une amélioration du rapport PAO2/FIO2 supérieur à 300 pour les patients intubés. Dans ces cas-là, il est recommandé de débuter la décroissance.

2. **Conduite à tenir chez les patients considérés comme non répondeurs à J4 et bénéficiant de trois jours supplémentaires à pleine dose (J4, J5, J6)**

   Si ces patients deviennent répondeurs selon les mêmes critères que précédemment à l'un de ces trois jours, il est recommandé d'entamer la décroissance de façon anticipée avant le J7, c'est-à-dire au J5 ou au J6. L'objectif est de ne pas sur-traiter des patients qui auraient une réponse nette à J5 ou à J6.

- Non répondeurs à D4 bénéficiant d'une amélioration nette à D5

D4	D5	D6
400 mg : 200 mg x2/j	200 mg : 100 mg x2/j	100 mg x1/j

- Non répondeurs à D4 bénéficiant d'une amélioration nette à D6

D4	D5	D6	D7
400 mg : 200 mg x2/j	400 mg : 200 mg x2/j	200 mg : 100 mg x2/j	100 mg x1/j

- Non répondeurs à D4 et en l'absence d'amélioration nette avant D7

D4	D5	D6	D7	D8
400 mg : 200 mg x2/j	400 mg : 200 mg x2/j	400 mg : 200 mg x2/j	200 mg : 100 mg x2/j	100 mg x1/j

3. Adaptation éventuelle des doses en fonction de la tolérance

- Réaction sévère à la perfusion : arrêt définitif du médicament,

- Neutropénie < 1000/mm^3 : arrêt transitoire du médicament. Contrôler 24 h après.
  - En cas de remontée des polynucléaires neutrophiles au-dessus de 1000/mm^3 : reprise de l'Anakinra à demi-dose.
  - En cas de persistance de la neutropénie inférieure à 1000 : arrêt définitif du médicament.

- ALAT > 5N : arrêt transitoire du médicament. Contrôler 24 h après.
  - En cas d'ALAT < 5N : reprise de l'Anakinra à demi-dose.
  - En cas de persistance d'ALAT > 5N : arrêt définitif du médicament.

- Diminution du débit de filtration glomérulaire au-dessous de 30 ml/mn selon la formule de Cockcroft ou formule de MRD :
  - Entre 15 et 3 ml/min : poursuite du médicament avec diminution des doses de 50 % et surveillance journalière de la fonction rénale.
  - En-dessous de 15 ml/min selon la formule de Cockcroft ou de MRD : arrêt transitoire du médicament et contrôle de la fonction rénale 24 h après.
    - Si persistance d'une clairance inférieure à 15 ml/min, arrêt définitif du médicament.
    - Si remontée de la clairance au-dessus de 15 ml/min reprise du médicament à demi-dose.

En cas de nécessité d'administration d'une demi-dose, il est demandé de ne réaliser qu'une seule des 2 perfusions prévues dans le schéma posologique soit :

- 200mg x1/jr
- Ou 100mg x1/jr en cas de décroissance débutée